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SPECIAL COMMUNICATION

Misoprostol for preventing and treating postpartum hemorrhage in the community: A closer look at the evidence

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ABSTRACT

The lack of clear interpretation of clinical and operational evidence on misoprostol use for postpartum hemorrhage (PPH) in the community may jeopardize the realization of its full potential for improving women's survival. This paper highlights the usefulness of misoprostol in addressing PPH in the community within the limits of available research evidence. There is now substantial evidence to support the beneficial effects of 600 μg of oral misoprostol for PPH prevention in the community, with a trend toward better protection against severe PPH morbidity, and particularly when administered by less skilled or lay caregivers. Although there is tangible evidence to show that 800 μg of sublingual misoprostol has important benefits for PPH treatment where there is no access to oxytocin, there is presently no direct evidence to indicate that less skilled or lay caregivers can safely use it to treat PPH in the community. Operational research evidence indicates that advance community distribution of misoprostol to pregnant women for postpartum self-use is a feasible strategy to ensure availability of the drug at the time of birth. The evidence is, however, limited by its quality to establish whether the benefits of such a strategy truly outweigh the potential harms. It is time for the international community to focus on improving PPH-related outcomes by scaling up what is currently guided by hard evidence and join forces to address unanswered questions through high-quality research.

1. Introduction

As the deadline for the United Nations' Millennium Declaration draws near, the persistently high burden of maternal ill health and death in low- and middle-income countries demands a revision of the strategies to improve women's survival by the international community. There is increasing interest in finding alternative ways to expand access to low-cost, evidence-based technology that could improve women's health in rural and hard-to-reach areas in low-resource countries. Tackling postpartum hemorrhage (PPH), the leading cause of maternal death, through such complementary strategies—from the preventive and treatment perspectives—has taken a top priority. It has become clear that after several decades of promoting the conventional uterotonics for PPH prevention and treatment, achieving the desired impact has remained challenging, as they are not available or feasible for use in all settings. This gap has drawn attention to misoprostol, a synthetic prostaglandin E_1 analog, which offers the opportunity to expand uterotonic coverage to settings where women rely only on physiologic control of postpartum blood loss.

Misoprostol is a potent uterotonic with some remarkable advantages over conventional uterotonics in resource-poor settings. It does not necessarily require skilled personnel for its administration since it is available in tablet form. It requires no cool storage facility to maintain its potency and is comparatively more stable at room temperature, thus has a long shelf life even in temperate climates. The adverse effects are frequent, but often do not require any treatment. Many international health bodies recommend misoprostol as a reliable alternative where oxytocin or ergometrine is not available or where their use is not feasible [1,2]. The World Health Organization (WHO) also acknowledged its critical role in improving maternal health by including it in its Model List of Essential Medicines for PPH prevention in 2011 [3]. These endorsements were the result of the growing body of research regarding the effectiveness, safety, and acceptability of misoprostol for PPH prevention and treatment.

Despite the consensus that misoprostol is a first-line alternative where conventional uterotonic use is not practicable, expanding its use to places where it could make a difference to women's survival has been slow. This unimpressive transition from research findings to clinical policies, programs, and practices has been attributed to many factors: its wide range of indications (including controversial ones such as abortion), its nonregistration for PPH in many countries, the lack of guidelines and provider training, concerns regarding its adverse effects, and misconceptions about the potential effects on promoting home births at the expense of institutional delivery [4]. Central to these challenges is the lack of clarity in the interpretation given to the available clinical and operational research evidence on misoprostol use for PPH in the community by various interest groups. While some are promoting unhindered rollout of misoprostol

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distribution programs from operational and feasibility standpoints [5–7], there are also those calling for caution based on insufficient evidence on the value and safety of such an approach [8,9]. The increasing volume of literature and sometimes conflicting evidence regarding misoprostol use for PPH in different settings has not helped matters. Getting past the obstacles limiting misoprostol's potential to effectively address the uterotonic coverage gap in the community requires reconsideration of the available answers to some fundamental research questions and presenting a balanced interpretation that is critical for decision making by policy makers. In the present paper, the evidence regarding misoprostol's effectiveness and safety in the community setting is summarized against the background of contextual issues relating to when and where it could be given, who could give it, and whether it is safe to provide it in advance to pregnant women for self-use after birth.

2. Is misoprostol effective and safe for preventing and treating PPH in the community (where there is no access to conventional uterotonics)?

2.1. Misoprostol for prevention

One reason for the initial hesitation in adopting misoprostol as a useful uterotonic agent is traceable to the results of earlier randomized controlled trials comparing misoprostol with no treatment in hospital settings. These trials conducted in the late 1990s and early 2000s showed inconsistent results regarding severe PPH and other indicators of blood loss with 400–600 μg oral or 400 μg rectal misoprostol [10–15]. This uncertainty has now been resolved with the results of 3 well-conducted and relatively large randomized controlled trials comparing 600 μg of oral or sublingual misoprostol with placebo in primary care or home delivery settings. These trials, which were conducted in Guinea Bissau [16], India [17], and Pakistan [18] between the mid- to late 2000s, consistently showed beneficial effects of misoprostol over no treatment for PPH prevention. A meta-analysis of the findings conducted for the present paper showed that misoprostol resulted in 24% and 41% reductions in the incidence of PPH (Fig. 1) and severe PPH (Fig. 2) compared with placebo, respectively. Subgroup analyses by the skill level of caregivers providing misoprostol in these studies indicate that the effects increased from that of uncertain benefits to 34% reduction for PPH (Fig. 1) and from 34% to 56% reduction for severe PPH (Fig. 2), between its administration by qualified midwives and lower-level health workers, respectively. These findings support the positive effects of misoprostol on PPH morbidity, particularly on heavy blood loss, and especially when used by less-skilled health providers in the community setting. What remains uncertain, however, is whether this improvement in PPH morbidity is sufficient to reduce the risk of maternal death in the community as the 3 trials collectively lack sufficient power to detect such a difference (1/1675 [0.06%] vs 1/1722 [0.06%]; RR 1.00, 95% CI, 0.14–7.07) (Fig. 3).

In view of the disparity between the findings of hospital- and community-based trials, it appears that the efficacy of misoprostol becomes apparent as one moves from hospital to primary care and home birth settings. It is reasonable to explain this heterogeneous finding by the variations in the available number and skills of caregivers in addition to routine care and delivery practices during the third stage of labor. Adjunct care and other precautionary measures during the third stage that are based on prelabor risk assessment are only likely in hospital settings where skilled professionals are available. It is possible that such added skills and care reduce the baseline risk of PPH and thus increase the sample size required to demonstrate beneficial effects of misoprostol. The potential effect of variation in delivery practices is demonstrated in the subgroup analyses of the community-based misoprostol versus placebo trials. The beneficial effect of misoprostol with respect to PPH (17% to 47% reduction; Fig. 4) and severe PPH (36% to 80%; Fig. 5) becomes more appreciable when the effect of misoprostol over placebo is compared between trials where caregivers were trained in and permitted to offer active management of third stage of labor (AMTSL) and those where expectant management was practiced. This differential effect has significant positive implications for settings where lower-level health workers without skills in AMTSL attend births.

With regard to safety concerns, women who receive misoprostol are likely to experience some adverse effects, notably shivering, pyrexia, and gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Three community-based placebo-controlled trials involving 3397 women [16–18] showed that misoprostol was associated with a very low incidence of vomiting (1.5%) and diarrhea (1.3%), which was similar to their frequencies in the placebo arm. It was, however, significantly associated with shivering (39.6% vs 14.0%; RR 2.77, 95% CI, 2.44–3.14) and pyrexia (6.9% vs 1.6%; RR 4.35, 95% CI, 2.88–6.57). These adverse effects are self-limiting and often subside with reassurance and symptomatic treatment that can be offered by lower-level caregivers. It is reassuring to note that severe maternal morbidity or maternal death was extremely rare, with 1 reported death among 1675 women (<0.1%) who received misoprostol in the 3 community-based trials, which is similar to that reported in hospital settings [19].

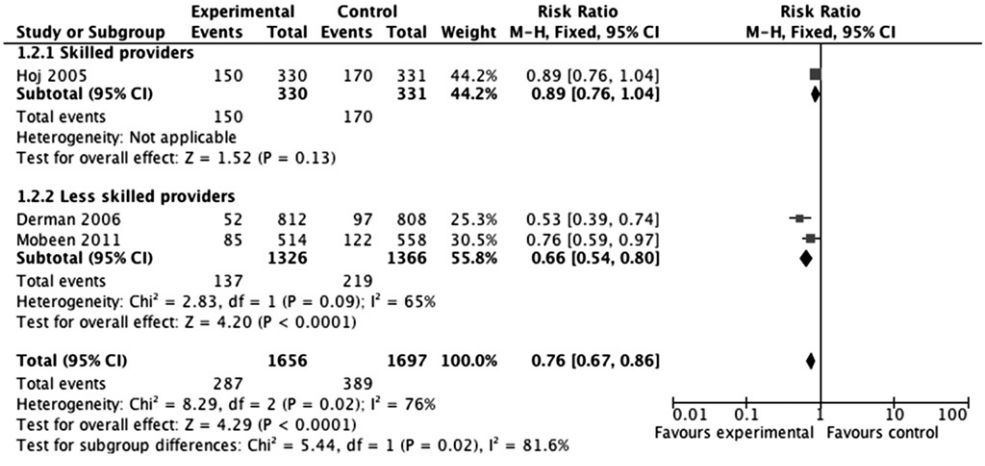

Fig. 1. Randomized trials of the effect of 600 μg of oral or sublingual misoprostol versus placebo on postpartum hemorrhage (blood loss >500 mL) in community/primary care settings, subgrouped by the skill level of caregivers.

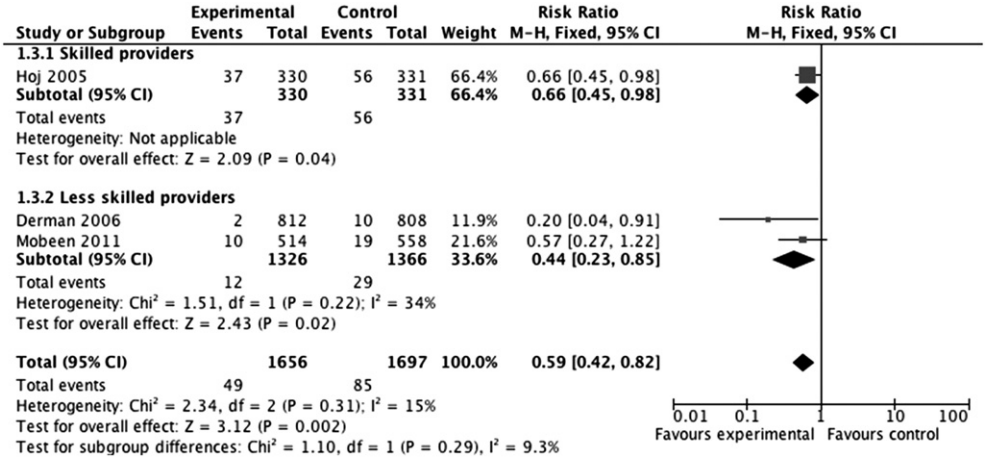

Fig. 2. Randomized trials of the effect of 600 μg of oral or sublingual misoprostol versus placebo on severe postpartum hemorrhage (blood loss > 1000 mL) in community/primary care settings, subgrouped by the skill level of caregivers.

2.2. Misoprostol for treatment

As expected, the evidence regarding the usefulness of misoprostol for PPH treatment in the community does not enjoy the same acceptance and confidence as its use for PPH prevention. This is mainly because treatment of PPH with uterotonics requires the skill to diagnose atonic PPH—a skill that is considered to be beyond the capacity of most caregivers at the community level. However, exploring other pragmatic treatment options for PPH in the community is valuable since intravenous oxytocin, the gold standard for PPH treatment, is an unrealistic choice in the short to medium term. Interestingly, a Cochrane review evaluating misoprostol as a treatment option for PPH included two hospital-based, placebo-controlled, randomized trials that assessed the effects of misoprostol in women who had received routine treatment with conventional oxytocics [20]. These trials showed some benefits regarding blood loss greater than or equal to 500 mL within 1 hour (RR 0.57; 95% CI, 0.34–0.96), but somewhat equivocal results with regard to the use of additional uterotonics, blood transfusion, evacuation of retained products, hysterectomies, and maternal death. Although the review authors concluded that there is insufficient evidence to demonstrate the benefits of such intervention, the findings would have had little value in a community setting where initial treatment of PPH with conventional uterotonics is not feasible, even if it did.

While the best evidence regarding the value of misoprostol for PPH treatment in the community could be derived from randomized controlled trials comparing misoprostol with placebo or usual care in such a setting, such a trial has yet to be conducted. This is not surprising considering the logistic and ethical challenges that such a trial would face. Therefore, evidence on the usefulness of misoprostol for PPH treatment has been largely from a recent hospital-based randomized trial involving 978 women diagnosed with PPH in Ecuador, Egypt, and Vietnam that assessed the noninferiority of 800 μg of sublingual misoprostol to intravenous oxytocin in women who had not been previously exposed to oxytocin [21]. The findings showed that active bleeding was controlled within 20 minutes in 440 (90%) women given misoprostol alone and 468 (96%) given oxytocin (RR 0.94; 95% CI, 0.91–0.98); additional blood loss of 300 mL or greater after treatment occurred in 147 (30%) women receiving misoprostol and 83 (17%) receiving oxytocin (RR 1.78; 95% CI, 1.40–2.26). Although the study showed that oxytocin is clearly more effective than misoprostol for PPH treatment, it expressed the potential performance of misoprostol compared with no treatment and identified its suitability as a first-line treatment alternative where oxytocin use is not feasible.

Safety concerns regarding the tested dose of misoprostol for PPH treatment in the community can be evaluated within the context of the same noninferiority trial [21]. Nausea and vomiting were more common with the 800-μg dose than expected with the 600-μg dose, occurring in 15% and 5%, respectively. Shivering occurred in 47% and fever in 44% of women who received misoprostol for treatment, which was close to 3 and 8 times as frequent, respectively, as in those who received intravenous oxytocin. While these adverse effects might cause considerable discomfort for the women, none of them was life threatening. It is reassuring to note that there were no hysterectomies or maternal deaths among women in both comparison groups. Compared with the consequences of PPH, these common adverse effects may be an acceptable price to pay in settings where no other option currently exists.

3. Should misoprostol be used in the community setting as a substitute for conventional uterotonics?

It is important to consider this question as situations may arise where the choice of misoprostol might be considered an attractive option for its logistical advantages even when oxytocin or ergometrine is available. A recently updated Cochrane review that included

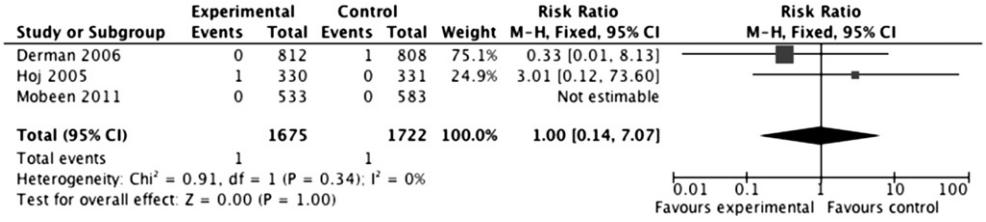

Fig. 3. Randomized trials of the effect of 600 μg of oral or sublingual misoprostol versus placebo on maternal death in community/primary care settings.

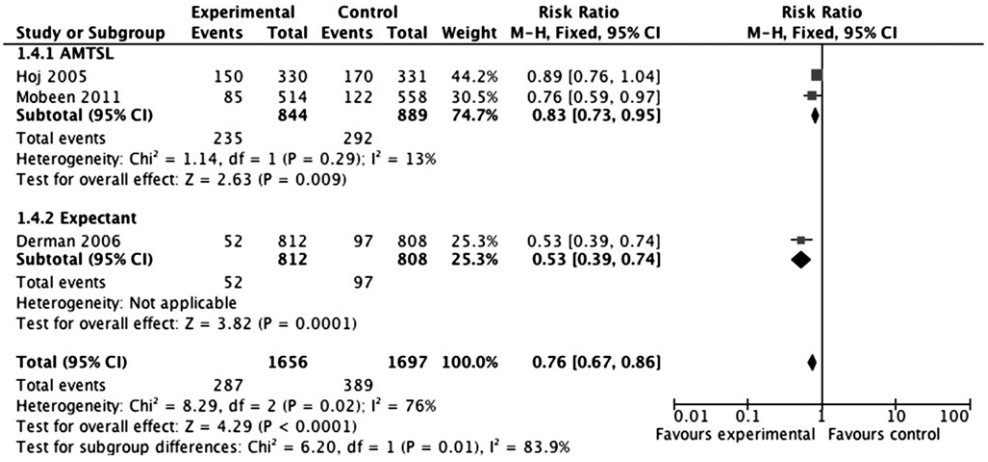

Fig. 4. Randomized trials of the effect of 600 μg of oral or sublingual misoprostol versus placebo on postpartum hemorrhage (blood loss >500 mL) in community/primary care settings, subgrouped by the third stage of labor practice.

17 randomized controlled trials involving 29 797 women comparing between 400 μg and 600 μg of oral misoprostol with oxytocin, ergometrine, or a fixed-dose combination of the two showed that there is excess risk of severe PPH with misoprostol (3.3% vs 2.4%; RR 1.33, 95% CI, 1.16–1.52) although misoprostol demonstrated a trend toward lowered risk of blood transfusion (RR 0.84; 95% CI, 0.66–1.06) [22]. There was no difference between the comparison groups with respect to other indicators of blood loss severity such as the use of additional uterotonics, postpartum hemoglobin, and manual removal of the placenta. Misoprostol was associated with significantly increased adverse effects, notably severe shivering (RR 7.24; 95% CI, 4.74–11.08) and pyrexia (≥38 degrees) (RR 6.68; 95% CI, 3.74–11.93). While these trials were essentially hospital based, the quality of the evidence is sufficient to discourage further studies on this question in any other setting.

4. Should lower-level caregivers administer misoprostol to: (a) prevent; and (b) treat PPH in a community setting?

One of the main advantages of misoprostol over the conventional uterotonics is that it is available in tablet form and thus can be administered by less-skilled providers. The recommended dose for PPH prevention and treatment is not dependent on the woman's weight and can easily be specified in terms of the number of tablets at the dispensing point. A large systematic review of lay health workers' delivery of health interventions to improve maternal, newborn, and child outcomes did not identify any studies that assessed the effects of lay health workers or trained traditional birth attendants (TBAs) administering misoprostol for PPH prevention or treatment compared with other cadres or no care [23]. However, two of the trials that demonstrated the positive effects of oral misoprostol compared with placebo in a community setting provide indirect evidence that trained TBAs and auxiliary nurse midwives could safely administer misoprostol for PPH prevention with good effects [17,18]. A double-blind randomized controlled trial from rural Gambia where trained TBAs provided either oral misoprostol or 0.2 mg ergometrine for PPH prevention at home births also supports this indirect evidence [24]. While these trials did not assess the effectiveness of lower-level caregivers' use of misoprostol for PPH prevention compared with other cadre or no approach, it is reassuring that they showed no adverse events attributable to this service delivery model. In addition, unlike the parenteral method of administration that could by itself compromise drug effectiveness or cause complications when given without necessary skills and precautions, the oral method poses no specific danger. Given that there are no concerns about lay health workers' need to make any diagnosis to use misoprostol for PPH prevention or the need for special skills to identify and manage its potential adverse effects, the indirect evidence suffices in guiding future recommendations and policy formulation. These explanations should provide enough confidence for the international health community

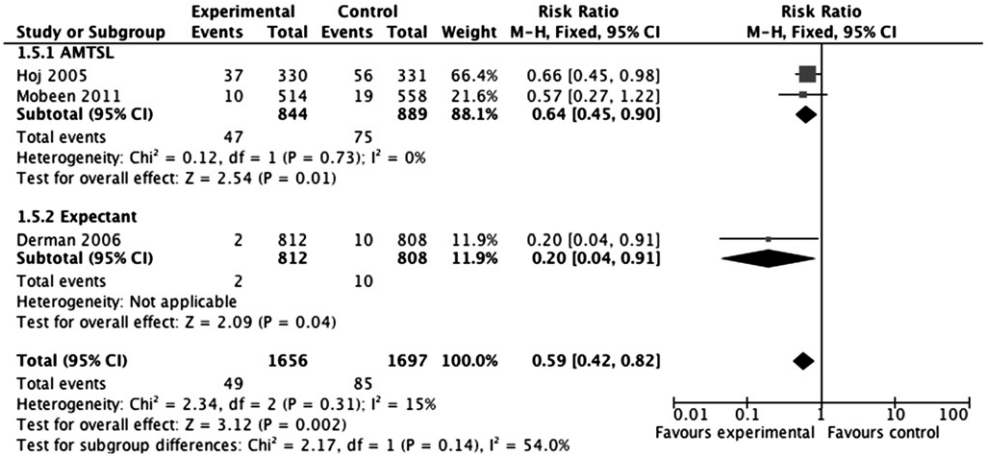

Fig. 5. Randomized trials of the effect of 600 μg of oral or sublingual misoprostol versus placebo on severe postpartum hemorrhage (blood loss >1000 mL) in community/primary care settings, subgrouped by the third stage of labor practice.

to move beyond the controversy surrounding lower-level caregivers administering misoprostol for PPH prevention. Recent developments suggest that this service delivery model is becoming increasingly acceptable by stakeholders and it is likely that the use of misoprostol by community healthcare providers and trained lay health workers would soon feature in international recommendations for PPH prevention.

For PPH treatment, there is no direct evidence on the effectiveness or acceptability of using lay health workers to administer misoprostol compared with usual care. There is also no reliable indirect evidence as the findings supporting the value of misoprostol in treating hemorrhage were conducted in hospitals with skilled professionals. The main concern with using this approach relates to the need for skill to accurately diagnose atonic PPH by lower-level providers, which cannot be guaranteed even with training. In a field intervention trial in Kigoma, Tanzania, TBAs were trained to diagnose PPH (using a locally adapted measure that roughly estimated blood loss) and treat with 1000 μg of rectal misoprostol [25]. These TBAs were reported to diagnose PPH satisfactorily at both comparison sites and those in intervention sites used rectal misoprostol to effectively treat PPH with consequent reduction in referral to a health facility. The study provides somewhat indirect and context-specific evidence on trained lower-level caregivers' potential to use misoprostol for PPH treatment. For it to be applicable and useful to other settings, this crude assessment of PPH by lay caregivers first needs to be validated. While it appears plausible that the desirable consequences of less-trained caregivers using misoprostol for PPH treatment probably outweighs the undesirable results, concerns about misguided delays in referral for non-atonic PPH are likely to remain an obstacle to international acceptance of this model for improving women's survival. Although this model may be acceptable and feasible under certain conditions, it might be wise at the moment to consider this option only in the context of rigorous research in places where an effective lay caregivers' program with a vibrant referral system already exist and where misoprostol use can be closely monitored with relevant indicators.

5. Should misoprostol be distributed to women during prenatal care for self-administration following childbirth?

The growing body of research demonstrating the effectiveness of misoprostol for PPH prevention in the community setting has paved the way for evaluation of different service delivery models to maximize its potential in underserved populations. Perhaps the most controversial of these operational techniques is advance community distribution of misoprostol to prenatal women for self-administration following childbirth. This strategy was borne out of the fact that as a result of cultural, physical, or geographical barriers to access to skilled delivery care, many pregnant women in remote and rural hard-to-reach areas of the world would deliver at home in the presence of a family member or at most an unskilled attendant. Advance provision of misoprostol to pregnant women themselves for self-administration has the potential to save lives where no uterotonic coverage exists, but also risks inappropriate use before birth or for other indications.

To date, there are two published studies that have evaluated the benefits and potential risks of community distribution of misoprostol for PPH prevention by self-administration. The first was a "nonrandomized, community experimental control study" in rural Afghanistan that evaluated the feasibility, acceptability, and programmatic effectiveness of a strategy of community education on PPH prevention accompanied by advance provision of misoprostol directly to prenatal women for self-administration following childbirth [6]. The second was an uncontrolled before–after operation research in Nepal that investigated the feasibility, acceptability, and safety of community-based distribution of misoprostol to pregnant women [5]. The two studies demonstrated that acceptance and self-use of misoprostol for PPH prevention by a large number of pregnant women are feasible. They also showed that incorrect use or misuse is extremely rare (<1%) and that over 60% increase in uterotonic coverage (misoprostol plus oxytocin) can be achieved through the strategy. These studies have been the basis for implementing similar programs in other countries such as India, Indonesia, Kenya, Mozambique, Nigeria, and Tanzania.

However, making recommendations on health system policies according to current standards requires the consideration of the quality of evidence on priority outcomes, magnitude of effects, balance between benefits and harms, values and preferences, and resource use, in addition to the feasibility of the intervention (the GRADE approach). A recent Cochrane review assessing the benefits and risks of a strategy of advance community distribution of misoprostol identified no randomized or quasi-randomized trials to support this strategy of rolling out misoprostol [26]. As nonrandomized studies can also provide good evidence, particularly where the research question poses significant logistical and financial challenges to be explored in a randomized trial, an assessment of the Afghanistan and Nepal studies is important to understand whether they are sufficient to drive policies. Evaluation of the characteristics for the two studies (not shown) indicated that the community interventions were robust and outcome measures of interest were essentially important feasibility and programmatic effectiveness outcomes. Both studies did not set out to assess misoprostol efficacy in the context of advance distribution and therefore did not objectively report outcomes related to blood loss or other indicators of severe morbidity. Although both studies provided information on adverse events and maternal death, only the Nepal study included maternal death as part of safety outcomes a priori. Assessment of the risk of bias (not shown) indicated that as a result of the inherent limitations of their designs, both studies were at high risk of bias at multiple levels. Using the GRADE approach, study limitations such as high risk of selection and confounding biases and potential effects of unmeasured co-interventions as identified in these studies are likely to generate between "low" to "very low" quality evidence for the relevant outcomes and may likely weaken the strength of the corresponding recommendation.

The two studies were conceived against the background of misoprostol's proven effectiveness and safety in the community and therefore disregarded some priority outcomes that are also critical for decision making for women, clinicians, and policy makers. This concept assumed that misoprostol administered by trained caregivers (as in the community misoprostol trials) is as effective and safe as that self-administered by the woman herself immediately after childbirth. This assumption may not be true as it ignores the potential effects of the "advance distribution" and "self-administration" components of the intervention as well as the problems that could arise if the woman develops adverse effects. An individually randomized placebo-controlled trial of advance distribution of misoprostol is currently in progress to clarify these issues. What is clear at the moment is that the strategy of advance distribution in resource-poor settings is effective in ensuring a dramatic increase in the proportion of women having misoprostol available at birth. The benefits regarding the overall improvement in delivery outcomes for women, however, remain uncertain given that none of these studies could reliably demonstrate any effect on severe morbidity or maternal death despite the large number of women recruited. In view of the huge resources required to roll out this strategy, it is appropriate to first determine if this approach is better than usual (or standard) care in these settings at an individual level before testing it in more rigorous community-level studies.

6. Conclusion

Misoprostol is arguably the most studied drug in sexual and reproductive health since the early 1990s. Its use for PPH prevention and treatment is likely to be the most useful, yet this remains its main

area of controversy. There is now substantial evidence to show that misoprostol is better than no treatment when used for prevention or treatment of PPH. Tangible indirect evidence also exists to support trained lower-level health providers, including TBAs, to safely and effectively administer misoprostol for PPH prevention. There are still concerns about the competence of lower-level health providers to safely diagnose and treat PPH in the community as the evidence base is weak. While efforts are being made to ascertain how low the skill level of the birth attendant should be to be able to treat PPH with misoprostol, it may be wise for the international community to focus on strategies that ensure that lower-level and lay caregivers are trained to increase uterotonic coverage for PPH prevention at the time of birth. As the saying goes, "prevention is better than cure". In our global drive to prevent PPH-related sufferings and deaths in the remote regions of the world, it is the responsibility of the scientific community to ensure that international standards of generating and applying evidence are not compromised. Health equity can only be achieved by providing interventions with clear benefits to women who have no power to choose.

Conflict of interest

The author has no conflicts of interest.

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References

[1] International Confederation of Midwives, International Federation of Gynecology and Obstetrics. Prevention and Treatment of Postpartum Haemorrhage: New Advances for Low Resource Settings. Joint Statement. Int J Gynecol Obstet 2007;97(2):160-3.
[2] World Health Organization. WHO Recommendations for the Prevention of Postpartum Haemorrhage. Geneva: WHO; 2007. Available at: http://whqlibdoc.who.int/hq/2007/WHO_MPS_07.06_eng.pdf.
[3] World Health Organization. WHO Model Lists of Essential Medicines. 17th edition. March 2011. Available at: http://www.who.int/medicines/publications/essentialmedicines/en/.
[4] Starrs A, Winikoff B. Misoprostol for postpartum hemorrhage: moving from evidence to practice. Int J Gynecol Obstet 2011;116(1):1-3.
[5] Rajbhandari S, Hodgins S, Sanghvi H, McPherson R, Pradhan YV, Baqui AH, et al. Expanding uterotonic protection following childbirth through community-based distribution of misoprostol: operations research study in Nepal. Int J Gynecol Obstet 2010;108(3):282-8.
[6] Sanghvi H, Ansari N, Prata NJ, Gibson H, Ehsan AT, Smith JM. Prevention of postpartum hemorrhage at home birth in Afghanistan. Int J Gynecol Obstet 2010;108(3):276-81.
[7] Potts M, Prata N, Sahin-Hodoglugil NN. Maternal mortality: one death every 7 min. Lancet 2010;375(9728):1762-3.
[8] World Health Organization. Clarifying WHO position on misoprostol use in the community to reduce maternal death. Geneva: WHO; 2010. Available at: http://whqlibdoc.who.int/hq/2010/WHO_RHR_10.11_eng.pdf.
[9] Gülmezoglu AM, Mathai M, Souza JP, d'Arcangues C, Mbizvo M. Misoprostol use in the community to reduce maternal death. Lancet 2010;376(9745):955.
[10] Hofmeyr GJ, Nikodem VC, de Jager M, Gelbart BR. A randomised placebo controlled trial of oral misoprostol in the third stage of labour. Br J Obstet Gynecol 1998;105(9):971-5.
[11] Hofmeyr GJ, Nikodem VC, de Jager M, Drakely A, Gelbart B. Oral misoprostol for labour third stage management: randomised assessment of side-effects (Part 2). Proceedings of the 17th Conference on Priorities in Perinatal Care; 1998. p. 53-4. South Africa.
[12] Hofmeyr GJ, Nikodem VC, de Jager M, Drakely A. Side-effects of oral misoprostol in the third stage of labour - a randomised placebo-controlled trial. S Afr Med J 2001;91(5):432-5.
[13] Bamigboye AA, Hofmeyr GJ, Merrell DA. Rectal misoprostol in the prevention of postpartum hemorrhage: a placebo-controlled trial. Am J Obstet Gynecol 1998;179(4):1043-6.
[14] Surbek DV, Fehr PM, Hosli I, Holzgreve W. Oral misoprostol for third stage of labor: a randomized placebo-controlled trial. Obstet Gynecol 1999;94(2):255-8.
[15] Benchimol M, Gondry J, Mention JE, Gagneur O, Boulanger JC. Role of misoprostol in the delivery outcome. [in French] J Gynecol Obstet Biol Reprod (Paris) 2001;30(6):576-83.
[16] Hoj L, Cardoso P, Nielsen BB, Hvidman L, Nielsen J, Aaby P. Effect of sublingual misoprostol on severe postpartum haemorrhage in a primary health centre in Guinea-Bissau: randomized double blind clinical trial. BMJ 2005;331(7519):723.
[17] Derman RJ, Kodkany BS, Goudar SS, Geller SE, Naik VA, Bellad MB, et al. Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomized controlled trial. Lancet 2006;368(9543):1248-53.
[18] Mobeen N, Durocher J, Zuberi NF, Jahan N, Blum J, Wasim S, et al. Administration of misoprostol by trained traditional birth attendants to prevent postpartum haemorrhage in homebirths in Pakistan: a randomised placebo-controlled trial. BJOG 2011;118(3):353-61.
[19] Hofmeyr GJ, Gülmezoglu AM, Novikova N, Linder V, Ferreira S, Piaggio G. Misoprostol to prevent and treat postpartum haemorrhage: a systematic review and meta-analysis of maternal deaths and dose-related effects. Bull World Health Organ 2009;87(9):666-77.
[20] Mousa HA, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev 2007(1):CD003249.
[21] Winikoff B, Dabash R, Durocher J, Darwish E, Nguyen TN, León W, et al. Treatment of post-partum haemorrhage with sublingual misoprostol versus oxytocin in women not exposed to oxytocin during labour: a double-blind, randomised, non-inferiority trial. Lancet 2010;375(9710):210-6.
[22] Tunçalp O, Hofmeyr GJ, Gulmezoglu AM. Prostaglandins for preventing postpartum haemorrhage. Cochrane Database Syst Rev 2007(3):CD000494 [Update: In Press].
[23] Lewin S, Munabi-Babigumira S, Glenton C, Daniels K, Bosch-Capblanch X, van Wyk BE, et al. Lay health workers in primary and community health care for maternal and child health and the management of infectious diseases. Cochrane Database Syst Rev 2010(3):CD004015.
[24] Walraven G, Blum J, Dampha Y, Sowe M, Morison L, Winikoff B, et al. Misoprostol in the management of the third stage of labour in the home delivery setting in rural Gambia; a randomised controlled trial. BJOG 2005;112(9):1277-83.
[25] Prata N, Mbaruku G, Campbell M, Potts M, Vahidnia F. Controlling postpartum hemorrhage after homebirths in Tanzania. Int J Gynecol Obstet 2005;90(1):51-5.
[26] Oladapo OT, Fawole B, Blum J, Abalos E. Advance misoprostol distribution for preventing and treating postpartum haemorrhage. Cochrane Database Syst Rev 2012(2):CD009336.